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Respiratory subtype of relapsing polychondritis frequently presents as difficult asthma: a descriptive study of respiratory involvement in relapsing polychondritis with 13 patients from a single UK centre

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ABSTRACT

Introduction: Relapsing polychondritis is a rare multisystem vasculitis characterised by recurrent cartilage inflammation. Respiratory involvement, of which tracheobronchomalacia (TBM) is the commonest form, is difficult to treat and is linked to increased mortality. We describe 13 patients with respiratory involvement.

Methods: This is a retrospective study of all the patients with relapsing polychondritis at University Hospitals Coventry and Warwickshire NHS Trust (UHCW), a secondary care provider for ~500 000. Only patients with respiratory involvement were included in this study.

Results: We identified 13 patients who fulfilled the inclusion criteria. Most patients were identified from the "difficult asthma" clinic. TBM was seen in 11 patients, whilst two patients had pleural effusions which resolved with immunosuppression and one patient had small airways disease. Computed tomography scans (inspiratory and expiratory) and bronchoscopy findings were useful in diagnosing TBM. Pulmonary function testing revealed significant expiratory flow abnormalities. All patients were treated with corticosteroids/disease-modifying anti-rheumatic drugs (DMARDs) and some were given cyclophosphamide or biological agents, although the response to cyclophosphamide (1 out of 4) or biologicals (2 out of 4) was modest in this cohort. Ambulatory continuous positive airway pressure ventilation was successful in four patients.

Conclusions: Relapsing polychondritis may be overlooked in "difficult asthma" clinics with patients having TBM (not asthma) and other features of relapsing polychondritis. Awareness of this condition is crucial to enable early diagnosis and interventions to reduce the risk of life-threatening airway collapse. A number of patients respond well to DMARDs and are able to minimise corticosteroid use.

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Tracheobronchomalacia can present as "difficult asthma" and can be associated with relapsing polychondritis. Optimal management of relapsing polychondritis is through medical treatments and support for the damaged airway through positive airway pressure. https://bit.ly/2JGoq23

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Introduction

Relapsing polychondritis was described by Pearson *et al.* [1] in 1960 as a rare multisystem disease characterised by recurrent episodes of inflammation and subsequent degeneration of cartilage and connective tissue throughout the body. Relapsing polychondritis most commonly affects the respiratory tract, nose, ears and joints [1–4]. McAdam *et al.* [3] described six classical features of relapsing polychondritis, namely bilateral auricular chondritis, nasal chondritis, respiratory tract chondritis, seronegative inflammatory arthritis, ocular inflammation and audiovestibular damage. McAdam's diagnostic criteria needed three out of six of the aforementioned clinical features for confirmation of diagnosis. Additional diagnostic criteria were developed by Damiani *et al.* [5] and Michet *et al.* [2]. Both of these groups have developed A and B criteria with Damiani criteria keeping all six primary clinical features as A criteria and additionally including histological confirmation as a B criterion and response to corticosteroids or dapsone as a C criterion. Three A criteria or one A and B, or two A with C are needed for diagnosis. Michet criteria include nasal, auricular and laryngotracheal cartilage inflammation as A criteria with the rest as B criteria, and two A or one A and two B criteria are needed for diagnosis.

Respiratory tract chondritis is thought to affect up to 50% of patients during the course of their disease [2, 3, 6] and remains the primary cause of mortality in relapsing polychondritis [3]. Patients often experience airway symptoms such as dyspnoea, cough, chest discomfort, hoarseness, stridor [7] and even complete aphonia in some cases [4] due to inflammatory oedema of the larynx, trachea and bronchi. The underlying chronic cartilage inflammation in the tracheobronchial tree leads to tracheomalacia [8]; or tracheobronchomalacia (TBM) when this extends to one or both primary bronchi. Both phenomena can result in exaggerated airway narrowing during expiration and widening during inspiration [9–11], demonstrable in pulmonary function tests and computed tomography (CT) scans of the chest. Unless early diagnosis and appropriate medical or surgical interventions are in place, the progressive cartilage destruction in the airways due to recurrent cartilaginous inflammation may ultimately result in life-threatening airway obstruction and dynamic airway collapse [12]. Relapsing polychondritis can involve the eyes, neurological system, heart and blood vessels, and there is an association with the HLA DR4 allele [13]. Respiratory problems can be particularly difficult to treat, and very little data exist to guide us with regards to optimal screening and assessment modalities for tracheomalacia or TBM. Management of these patients continues to remain a challenge, and the diagnostic delay can often result in significant damage, which necessitates long-term mechanical support through stents or pneumatic support through continuous positive airway pressure (CPAP) [14, 15]. Despite best treatment, patients are often left with substantial life-changing disability.

We describe a series of patients with relapsing polychondritis all of whom had respiratory involvement. Most had presented to respiratory clinics or had been admitted to hospital with severe shortness of breath. All patients attended University Hospital Coventry and Warwickshire NHS Trust, which is based in Coventry in the West Midlands in the UK and is a secondary care provider for a population of around 500 000. This case series describes the respiratory manifestations and aims to increase the awareness of relapsing polychondritis in patients presenting with respiratory symptoms, particularly in individuals who appear to have oral corticosteroid-dependent asthma.

Materials and methods

We reviewed the medical records of 13 patients with relapsing polychondritis, all of whom had respiratory involvement. Patients were identified through the respiratory and rheumatology clinics at a single centre between 2013 and 2018, and patients were often seen together in a combined clinic. The diagnosis of relapsing polychondritis was made clinically using the clinical diagnostic criteria [2, 3, 5]. Disease activity was assessed using the Relapsing Polychondritis Disease Activity Index (RPDAI) which includes scoring on each organ that can be affected by relapsing polychondritis as well as C-reactive protein (CRP) [16]. There are 28 different items with scores ranging from 1 to 24. Respiratory chondritis scores 14 without and 24 with respiratory failure and is the highest scoring item in RPDAI. Patients' demographic characteristics, clinical features, diagnostic test results and therapeutic interventions were noted. The database was set up in 2016 and details of patients were updated regularly. Ethical approval was obtained

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TABLE 1 Clinical features of patients with relapsing polychondritis

Patient	Sex	Age years	Comorbidities	BAC	NC	RTC	SP	OI	AD	Response to corticosteroids	TBM proven
1	M	65	T2DM, hypothyroid, psoriasis	Y	Y	Y	N	Y	N	Y	Y
2	F	70	Memory loss	N	Y	Y	Y	N	N	Y	Y
3	F	50	T2DM	Y	Y	Y	Y	N	Y	Y	Y
4	F	53	Hypothyroid, fibromyalgia, HTN, Behçet's, obesity	Y	Y	Y	Y	N	N	Y	Y
5	F	76	Previous TB, immunodeficiency, HTN, T2DM, OA	N	N	Y	Y	N	Y	Y	Y
6	F	74	HTN, angina, AF, T2DM, antiphospholipid antibodies	Y	Y	Y	Y	N	N	Y	Y
7	F	76	Emphysema	N	N	Y	N	N	N	Y	Y
8	F	70	HTN, obesity, acoustic neuroma, hyperlipidaemia	N	N	Y	Y	N	N	Y	Y
9	F	78	T2DM, obesity, MI, AF, CKD, dementia, asthma	Y	Y	Y	Y	N	Y	Y	Y
10	M	31	Hypoadrenalism, bronchiectasis	Y	Y	Y	Y	N	N	Y	Y
11	F	52	Obesity, COPD, ankylosing spondylitis, psoriasis	Y	Y	N	Y	N	Y	Y	N
12	M	79	Myelodysplasia, follicular lymphoma, osteoporosis	Y	N	Y	N	Y	N	Y	N
13	M	78	T2DM, IHD, CKD, myositis	N	N	Y	Y	N	Y	Y	Y

BAC: bilateral auricular chondritis; NC: nasal chondritis; RTC: respiratory tract chondritis; SP: seronegative polyarthritis; OI: ocular inflammation; AD: audiovestibular damage; TBM: tracheobronchomalacia; T2DM: type 2 diabetes mellitus; HTN: hypertension; TB: tuberculosis; OA: osteoarthritis; AF: atrial fibrillation; MI: myocardial infarction; CKD: chronic kidney disease; IHD: ischaemic heart disease.

from the Research and Development office within our Trust (approval number – GF 0267). Statistics are predominantly descriptive, and the Microsoft Excel program was used to assimilate the data.

Results

We identified 13 patients with relapsing polychondritis; all of these patients had respiratory involvement. We did not need to exclude any patients due to lack of respiratory involvement. Most of these patients (10 out of 13) were identified in "difficult asthma" clinics with two being diagnosed following an inpatient admission with acute shortness of breath and one diagnosed from a rheumatology clinic. The demographics are described in table 1. Male to female ratio was 1:3 with three males and nine females. The median age of the patients was 65 (range 28 to 76) years. Most patients had other comorbidities with diabetes being the commonest (five patients) and hypertension seen in four patients. Other autoimmune disorders were diagnosed in seven of these patients. Psoriasis and hypothyroidism were noted in two patients each. One patient had overlap with Behcet's disease (mouth and genital ulcers with inflamed cartilage – MAGIC syndrome), and another had ankylosing spondylitis (table 1, figures 1–5).

We found that eight patients (62%) had bilateral auricular chondritis and nasal chondritis, whilst 10 patients (77%) had seronegative polyarthropathy with two patients (15%) having ocular inflammation and

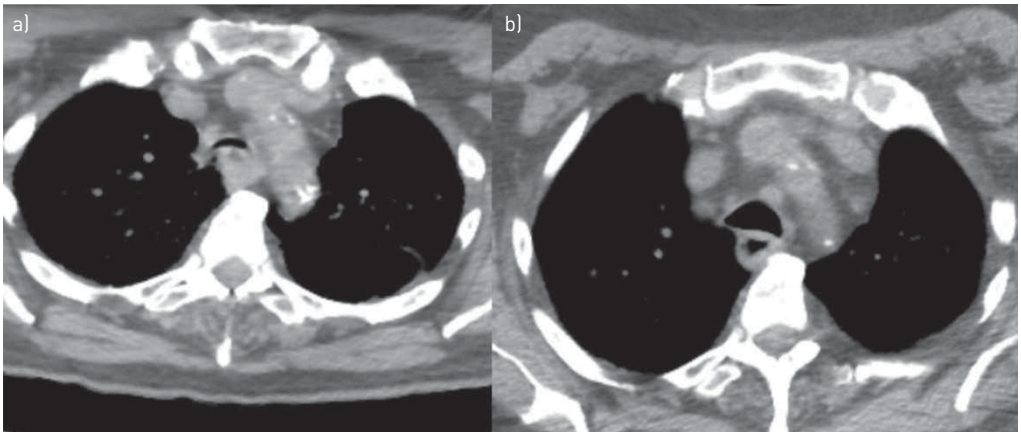

FIGURE 1 a) Admission computed tomography (CT) scan showing near complete collapse of trachea in a patient that was subsequently diagnosed with relapsing polychondritis. b) Repeat CT after intravenous corticosteroids with inspiratory and expiratory films showing significant improvement of tracheal narrowing (expiratory phase CT).

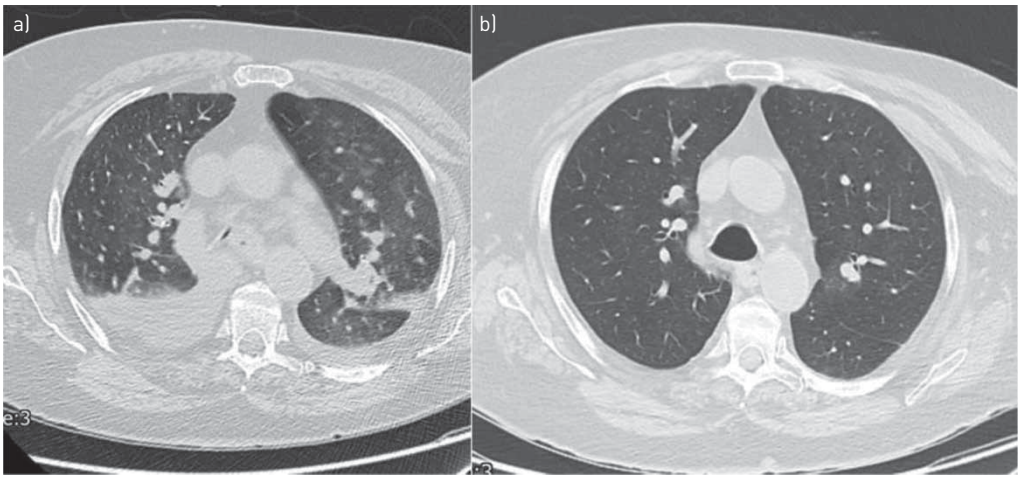

FIGURE 2 a) Patient with admission computed tomography (CT) chest showing near complete collapse of trachea and pleural effusions. b) Repeat CT after treatment with high-dose corticosteroids with improvement in trachea and resolution of pleural effusions.

FIGURE 3 Patient with collapse of trachea.

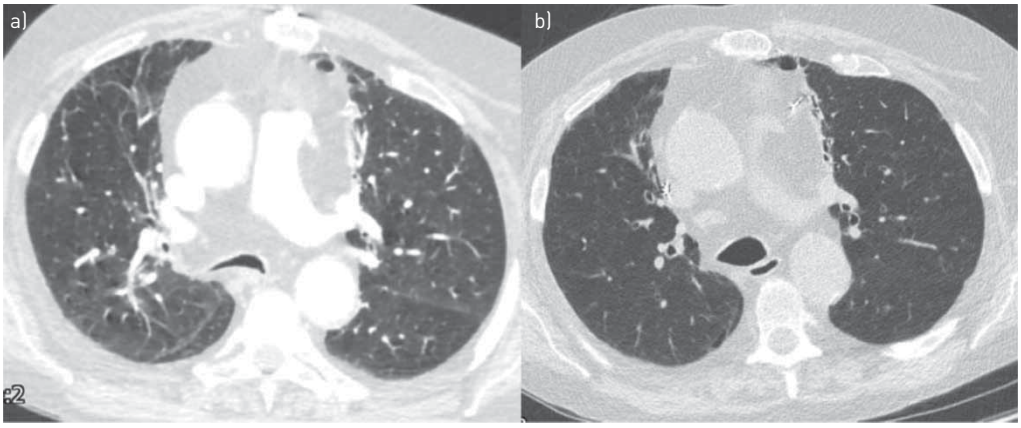

FIGURE 4 a) Patient with presentation computed tomography showing significant narrowing of trachea. b) Post-treatment imaging showing improvement in dimensions of trachea.

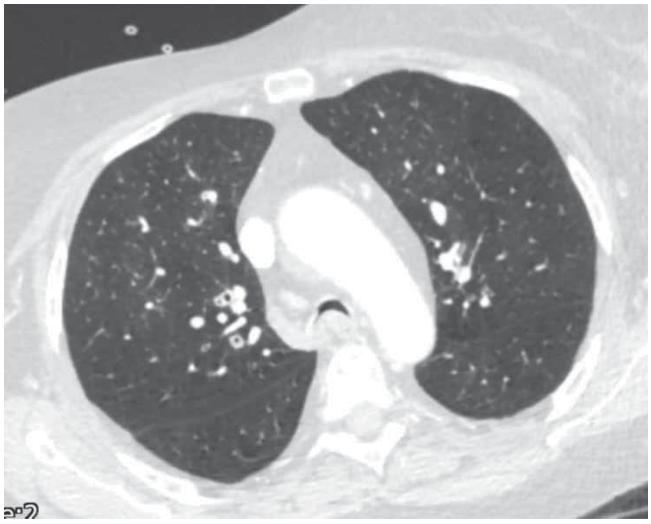

FIGURE 5 Pre-treatment tracheal collapse in a patient.

five patients (38%) had audiovestibular damage (figure 6). All patients had good response to oral prednisolone and fulfilled criteria for diagnosis of relapsing polychondritis (Damiani). Most patients (10 out of 13) were picked up from the difficult asthma clinics. All patients had wheeze and persistent cough and hence a diagnostic label of asthma, but it was the presence of monophonic wheeze, presence of inspiratory stridor in two patients, barking nature of cough in two patients and lack of classical reversibility and response to steroids that led to the suspicion of underlying more complex airway issues and possible expiratory airway collapsibility. Patients with good response to oral prednisolone demonstrated return of their signs and worsening of other symptoms with dosage reduction below 20 mg daily leading to further suspicion about the underlying diagnosis. Dynamic CT (inspiratory and expiratory) images were obtained along with flexible bronchoscopy. Bronchoscopy was performed in four patients. Mild sedation using intravenous midazolam and local analgesia with 2% lignocaine were instilled. Patients were able to cooperate and forcibly exhale. Views were taken from the proximal and distal trachea, right and left main bronchi and segmental bronchi during inspiration and forced expiration. Fifty per cent or more reduction in the cross-sectional area of the airway during the dynamic bronchoscopy and CT were used as the diagnostic cut-off for the diagnosis of TBM. Two of our patients demonstrated smooth thickening of the airway wall and luminal narrowing of the distal trachea and main bronchi, and one demonstrated symmetrical stenosis of the large airways, whereas the remaining patients had >50% reduction of the airway luminal area with crescentic appearance of the airway due to flattening of airway walls during expiration.

FIGURE 6 Patient images demonstrating auricular chondritis with inflammation of the external ear with sparing of non-cartilaginous part.

Although other features such as bilateral auricular chondritis or nasal chondritis had been present in eight patients, they had rarely complained about these symptoms to their clinicians as other symptoms, particularly severe breathlessness, were their primary concern. Eliciting these symptoms required direct questioning. One patient had classical nasal bridge collapse which they previously told several clinicians (*via* interpreters) was the result of childhood trauma, although on detailed questioning there was in fact no history of trauma. Seronegative inflammatory arthritis was a presenting feature in two patients (predominantly large joints) and had been noted in 10 patients.

Laboratory testing showed anaemia in seven patients and raised inflammatory markers including CRP or erythrocyte sedimentation rate in six patients. As a number of patients were on long-term corticosteroids for "difficult asthma", it was difficult to get accurate trends of inflammatory markers prior to treatment. None of the patients had evidence of eosinophilia at any point. Rheumatoid factor, anti-cyclic citrullinated antibodies, antinuclear antibodies, anti-double-stranded DNA antibodies and neutrophil cytoplasmic antibodies were all negative, although one patient had antiphospholipid antibodies. Chest radiographs were normal in 11 patients; two had shown features of pleural effusions and these were confirmed on CT scans later. None of the patients had any other features to suggest antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis.

In 12 out of 13 patients, flow-volume loops demonstrated flattening of either inspiratory or expiratory curves, or both. Flattening of the expiratory limbs in flow-volume loops was prevalent in most, suggesting large airway collapsibility during expiration (figures 7 and 8). There was no evidence of reversibility with β2 agonists in 11 patients, whilst one patient with small airway disease showed reversibility with likely coexistent asthma.

Treatment

Corticosteroids and conventional disease modifying agents

Corticosteroids were used in all patients, and disease-modifying anti-rheumatic drugs (DMARDs) such as methotrexate 15 to 25 mg weekly (6 patients), azathioprine 1–2.5 mg·kg·day^{-1} (2 patients) and mycophenolate mofetil 1–2 g daily (2 patients) were successful in reducing disease activity (table 2). One patient developed hypogammaglobulinaemia, which was thought to be secondary to immunosuppression and was treated with replacement intravenous immunoglobulin (IVIG) as she was having recurrent infections (predominantly chest infections). Prednisolone was usually started at 1 mg·kg·day^{-1} orally in patients with respiratory failure and 0.5 mg·kg·day^{-1} in patients without respiratory failure with gradual

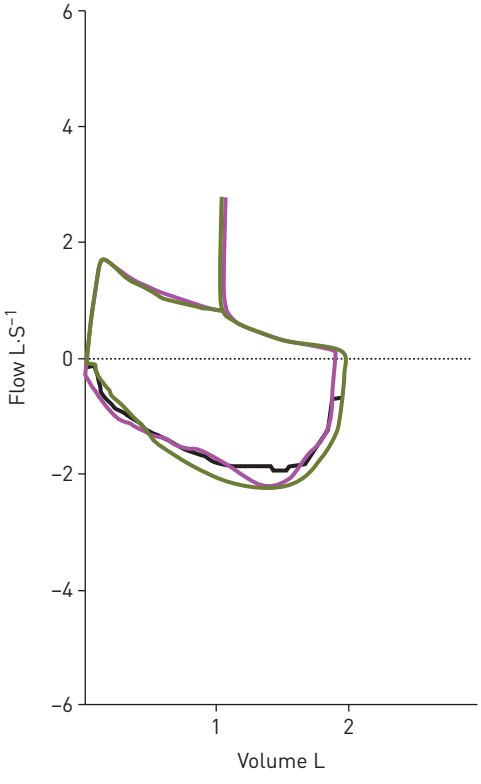

FIGURE 7 Flow–volume loop of patient 4 showing flattening of the expiratory limb and inspiratory limb to a lesser extent.

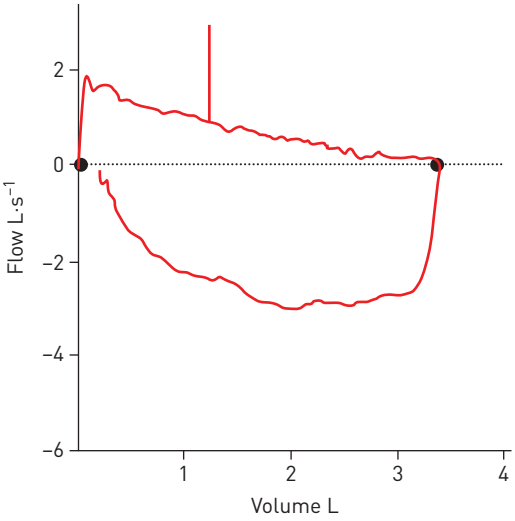

FIGURE 8 Flow–volume curve of patient 6 showing flattening of the expiratory limb and inspiratory limb to a lesser extent.

tapering every 2–4 weeks initially. Dose reduction was achieved in all cases, but four patients struggled to wean prednisolone dose down below 10 mg. In two patients, we used <20 mg prednisolone, as higher doses were not needed. Intravenous cyclophosphamide was used in four cases but was thought to be unsuccessful in three of these on the basis of lack of symptomatic benefit. Cyclophosphamide was only used after failure of conventional DMARDs and was used primarily for TBM.

Airway support

Patients with severe airway collapse >90% of airway area with disabling symptoms were considered for large airway stenting alongside medical therapies. Successful stenting was performed in three patients; in one other patient the stent had to be removed as it was exacerbating infections and in another due to continuous coughing. Six patients with moderately severe airway compromise (75–90%) and significant breathlessness on exertion were receiving intermittent ambulatory CPAP; two discontinued due to lack of tolerance. Noninvasive ventilation (NIV) was used with maximum inspiratory pressure (IPAP) of 24 and expiratory pressures (EPAP) of 10 cmH_2O whilst CPAP pressures were between 10 and 13 cmH_2O. Overnight sleep studies excluded significant sleep disordered breathing in these patients. Within this cohort, seven patients have had recurrent admissions for "flare of asthma" prior to the diagnosis with three of these not requiring further inpatient admissions once immunosuppression was instituted.

TABLE 2 Pharmacological and non-pharmacological treatment for patients with relapsing polychondritis

Patient	Sex	Age years	CPAP	Stent	IS drugs	Corticosteroid dose	Previous drugs	Baseline RPDAI
1	M	65	N	N	MTX		Pred	37
2	F	70	N	N	MMF, infliximab	Pred 5 mg	SSZ	27
3	F	50	DNT	N	MTX		Pred	45
4	F	53	Y	Y	MMF, MTX	Pred 10 mg	AZA, cyclophosphamide, ADA and ETN	47
5	F	76	Y	N	SSZ, HCQ, ABT, IVIG	Pred 7.5 mg	MTX, ETN, leflunomide, AZA	44
6	F	74	Y	Y	MTX, AZA	Pred 10 mg	Cyclophosphamide	43
7	F	76	Y	N	Cyclophosphamide	Pred 10 mg	MTX	27
8	F	70	N	N	AZA	Pred 5 mg		15
9	F	78	DNT	N		Pred 5 mg	MTX, AZA, HCQ	24
10	M	31	N	N		HCT 20/10/10		33
11	F	52	N	N	Secukinumab	Pred 10 mg	MTX, ETN, HCQ, cyclophosphamide, ADA	38
12	M	79	N	N		Pred 5 mg		35
13	M	78	Y	Y	MTX	Pred 5 mg	AZA	40

CPAP: continuous positive airway pressure; IS: immunosuppressant; RPDAI: Relapsing Polychondritis Activity Index; MTX: methotrexate; Pred: prednisolone; MMF: mycophenolate mofetil; SSZ: sulfasalazine; DNT: did not tolerate; AZA: azathioprine; ETN: etanercept; HCQ: hydroxychloroquine; ABT: abatacept; IVIG: intravenous immunoglobulin; HCT: hydrocortisone; ADA: adalimumab.

Biological DMARDs

Biological DMARDs were tried in four patients with anti-tumour necrosis factor (TNF) therapies being successful in one and unsuccessful in three patients (two due to inefficacy, another due to allergic reactions to both etanercept and adalimumab). Of the three patients who failed anti-TNF therapy, two were tried on other agents, with one patient responding well to abatacept whilst another patient was started on secukinumab for ankylosing spondylitis and had good response for spinal disease, but no change in RPDAI.

Eight patients are still under regular follow-up and have been under follow-up for >5 years since diagnosis, one has been lost to follow-up and four patients have died. In two of these cases, primary cause of death was chest infection; in the other two, it was unrelated causes, one from complications of myelodysplasia.

Discussion

A number of studies have described small numbers of patients with respiratory features and some have shown airway involvement to be the leading cause of death in relapsing polychondritis [1, 3, 6, 15, 17]. TBM has been reported in the literature in up to 50% of patients with relapsing polychondritis. Our series saw TBM as the commonest presentation of relapsing polychondritis, although it is quite likely that a number of patients with less serious problems might not have been appropriately diagnosed given the rarity of this condition. A French series reported 142 patients with relapsing polychondritis who formed three distinct patterns – haematological, respiratory and "mild" phenotypes [18]. Within the respiratory phenotype, which formed 22.5% of their series, auricular involvement was less common, something we have seen as well. Similar to our series, they found that these patients received more intensive treatment, were prone to infections and were frequently admitted to the intensive care unit. Our series provides more detail about the respiratory subtype of relapsing polychondritis with specific focus on presentation and management. We did not need to exclude any patients with relapsing polychondritis due to lack of respiratory involvement. Given its rarity, it is likely that there are other patients with less serious manifestations that have not reached rheumatology or respiratory clinics and have not been given the diagnosis yet. The majority of these patients were originally thought to have oral corticosteroid-dependent asthma, and once TBM was suspected or diagnosed, physicians started searching for and finding other features of relapsing polychondritis. Patients had not complained about the other manifestations such as chronic auricular chondritis or nasal chondritis as the symptom of breathlessness predominated.

Physical treatments of TBM with stenting and CPAP are well recognised [6–9, 17, 19]; however, there is very little information in the literature about pharmacological treatment of TBM through immunosuppression. This is important as TBM can be the only manifestation of relapsing polychondritis [20]. In our series, most patients had responded well to pharmacological therapy, although some needed stent insertion to support the bronchial tree. Stenting also had mixed results, and it is unclear as to whether there are specific features that would indicate use of stents in preference to drug therapy. Stenting is most likely to be useful after optimal control of active disease (to stabilise the damaged section of the tracheobronchial tree once medical treatment has controlled active inflammation). Complications following stenting are relatively common with one study showing 49 out of 58 patients having a complication, the commonest of which are stent migration, infection and partial obstruction [21]. Aggressive early management can be difficult to achieve when the patient has been symptomatic for so many years and airway damage has accumulated before the diagnosis is made. Intermittent ambulatory CPAP has been described previously with variable results [22–24]; our group has previously described successful use of CPAP in TBM. Such long-term use of portable NIV combined with overnight CPAP has not been reported to our knowledge. We have seen good symptomatic improvement and long-term stability with CPAP used in this fashion together with medical treatments.

Clinical and symptomatic evaluation, dynamic (inspiratory and expiratory) CT scans and flexible bronchoscopy were critical in establishing the diagnosis of TBM, which is consistent with reports from the literature [8–10]. Other features of relapsing polychondritis were identified clinically, although recent reports suggest positron emission tomography CT (PET CT) might be an additional resource for defining the severity and extent of disease [25]. PET CT has other potential advantages as it can: a) differentiate damage from active inflammation, and b) provide information about large vessel vasculitis and other organs that are not easy to assess clinically. We have not used this modality in our patients, and this could be evaluated in future studies.

The prevalence of relapsing polychondritis in Coventry appears to be at least 26 per million on the basis that we have 13 patients locally within our catchment area of around 500 000. If these prevalence data were true for the rest of the UK as well, one would expect roughly 1500 additional patients! It is difficult to estimate the true prevalence for a rare condition, and the literature has offered very wide estimates ranging between 3.5 per million to 23 per million. Hungarian data suggest similar numbers (23 per million) to the

numbers estimated here based on 233 cases from a population of 10 million [26]. Incidence in that study was around 3.5 per million patient years. Incidence of relapsing polychondritis in a UK study was 0.71 per million patient years and prevalence was estimated at 9 per million [27]. In Rochester (Minnesota, USA), the incidence of relapsing polychondritis was estimated at 3.5 per million [4]. Given the rarity of the condition and difficulty in diagnosis, it is not a surprise that there is such wide variation. This study provides new impetus to look for specific features of relapsing polychondritis that may have a major influence on incidence and prevalence estimates.

There are no controlled clinical trials in this area (as is the case for a number of rare diseases), and it may be possible to set up trials in this area if the prevalence is significantly higher than was previously thought. There is a need to increase awareness of this disease amongst all the specialties that are likely to come across these patients. Optimal management of these patients continues to remain a challenge. The exact pathogenesis is not clearly understood. Various immune processes that have been described include reduction of immunoregulatory cells, antibodies attacking cartilage tissue elements like type-II, type-IX and type-XI collagen and matrilin1, changes in cytokine profiles, deposition of immune complexes and insufficient tissue regeneration [28–34]. This makes it quite challenging when choosing drugs for refractory patients. Within our cohort, we observed some responses to DMARDs with methotrexate, azathioprine and mycophenolate being successful. In fact, in one patient we were able to completely stop corticosteroids and have not needed to go back to corticosteroids for >2 years. Responses to biological agents and *i.v.* cyclophosphamide have been modest in this cohort – this may be due to delay in diagnosis, which can sometimes be a number of years. Also, we have not routinely used *i.v.* cyclophosphamide for induction but tended to use it when other agents have failed. Disease activity and damage scores have been developed [16, 35] and are of use in documenting response to treatment; and also serve as a reminder of the various manifestations of this rare illness. Multiple biological agents have been tried, but due to the rarity of the condition, there are no randomised controlled trials in this field. A French national study looking at biologicals in relapsing polychondritis did not demonstrate any clear trends that would help guide use of biological agents [36].

Limitations

This is a retrospective review and studies of this sort are subject to systemic biases, which are applicable to this study. Prevalence data are affected by referral pathways and other biases which would be applicable to this study. Also, patients presenting with respiratory symptoms were selected, so this is a referral bias. There is also likely to be left censorship bias as some patients who may have died or were lost to follow-up would not have been included.

Conclusions

Relapsing polychondritis, although rare, with prevalent respiratory involvement may be the cause of significant morbidity and mortality. Patients might be misdiagnosed with other respiratory diseases in particular being labelled as "difficult asthma". There is an important need to recognise and diagnose relapsing polychondritis, as there are specific treatment options including DMARDs that these patients are likely to benefit from. Awareness of this condition is crucial to enable early diagnosis and clinical interventions to reduce the risk of life-threatening airway collapse.

Author contributions: All authors have contributed to the study design and write up. SD, CG, GP, AA, JS, ST have helped with data collection and analysis.

Data availability: Data collected as part of their standard care were used for this study. There were no additional interventions performed.

Conflict of interest: S. Dubey has nothing to disclose. C. Gelder has nothing to disclose. G. Pink has nothing to disclose. A. Ali has nothing to disclose. C. Taylor has nothing to disclose. J. Shakespeare has nothing to disclose. S. Townsend has nothing to disclose. P. Murphy reports grants paid to his institution and personal fees for CPD approved activity from Philips, ResMed, F&P and B&D Electromedical, advisory board fees from Santhera, and grants paid to his institution from GSK, outside the submitted work. N. Hart reports an unrestricted research grant for the OPIP Trial from Philips-Respironics, personal fees for a lecture at TOP Forum China from Philips-Respironics Lecture, and unrestricted research grants for the HoT-HMV Trial from RESMED and Philips-Respironics, outside the submitted work; in addition, he has a European patent issued and a US patent pending for MYOTRACE. His research group has received unrestricted grants (managed by Guy's & St Thomas' Foundation Trust) from Philips and Resmed. Philips are contributing to the development of the MYOTRACE technology. D. D'Cruz has nothing to disclose.

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